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Cost-Effectiveness Analysis of Hepatitis B Immunization in Vietnam: Application of Cost-Effectiveness Affordability Curves in Health Care Decision Making

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A B S T R A C T

Objectives: To perform a cost-effectiveness analysis and to identify the cost-effectiveness affordability levels for a newborn universal vaccination program against hepatitis B virus (HBV) in Vietnam. **Methods:** By using a Markov model, we simulated a Vietnamese birth cohort using 1,639,000 newborns in 2002 and estimated the incremental cost-effectiveness ratios for quality-adjusted life-year gained following universal newborn HBV vaccination. Two types of analyses were performed, including and excluding expenditures on the treatment of chronic hepatitis B and its complications. We used Monte Carlo simulations to examine cost-effectiveness acceptability and affordability from the payer's perspective and constructed a cost-effectiveness affordability curve to assess the costs and health effects of the program. **Results:** In the base-case analysis, newborn universal HBV vaccination reduced the carrier rate by 58% at a cost of US $42 per carrier averted. From the payer's perspective, incremental cost-effectiveness ratio per quality-adjusted life-year gained was US $3.77, much lower than the 2002 per-capita gross domestic product of US $440. Vaccination could potentially be affordable starting at a US $2.1 million budget. At the cost-effectiveness threshold of US $3.77 per quality-adjusted life-year and an annual budget of US $5.9 million, the probability that vaccination will be both cost-effective and affordable was 21%. **Conclusions:** Universal newborn HBV vaccination is highly cost-effective in Vietnam. In low-income, high-endemic countries, where funds are limited and the economic results are uncertain, our findings on the cost-effectiveness affordability options may assist decision makers in proper health investments.

Keywords: acceptability, affordability, cost-effectiveness, incremental cost-effectiveness ratio, quality-adjusted life-year.

Introduction

The hepatitis B virus (HBV) is one of the most prevalent bloodborne viruses worldwide and is a major cause of chronic liver diseases and hepatocellular carcinoma [1,2]. It is an important public health problem for developing countries where the endemicity is generally high. Currently, about 350 million people worldwide are chronic HBV carriers, as demonstrated by the presence of hepatitis B surface antigen for more than 6 months [3]. These individuals are at a much higher risk of liver damage; 15% to 40% of the infected patients eventually develop cirrhosis, liver failure, or hepatocellular carcinoma, contributing to more than 1 million deaths annually [1,4,5]. Epidemiological studies have reported that the prevalence of chronic hepatitis B (CHB) surface antigen carriers is between 8.8% and 20.5% across different populations and regions in Vietnam [6,7]. With a population of 86 million in 2010, there would be more than 7.5 million people at risk of premature death due to HBV infections in Vietnam.

Universal newborn HBV vaccination could be a feasible and effective solution for preventing HBV infection and a cost-effective prevention in the developing world [8,9]. In Vietnam, hepatitis B vaccine was first introduced into the Expanded Program of Immunization in 1997, but universal HBV vaccination was not completed until mid-2003 with the support from the Global Alliance for Vaccines and Immunizations starting in 2002 [10]. To date, data are lacking regarding the impact of universal newborn vaccination in Vietnam from a health-economic perspective. While cost-effectiveness analyses of universal HBV vaccination have been extensively performed for many developed countries, such analyses are still scarce for the developing world [9].

To aid allocation decisions on scarce health care resources, it is important to assess the cost-effectiveness of any large-scale prevention programs, which require substantial resources. In this ar-

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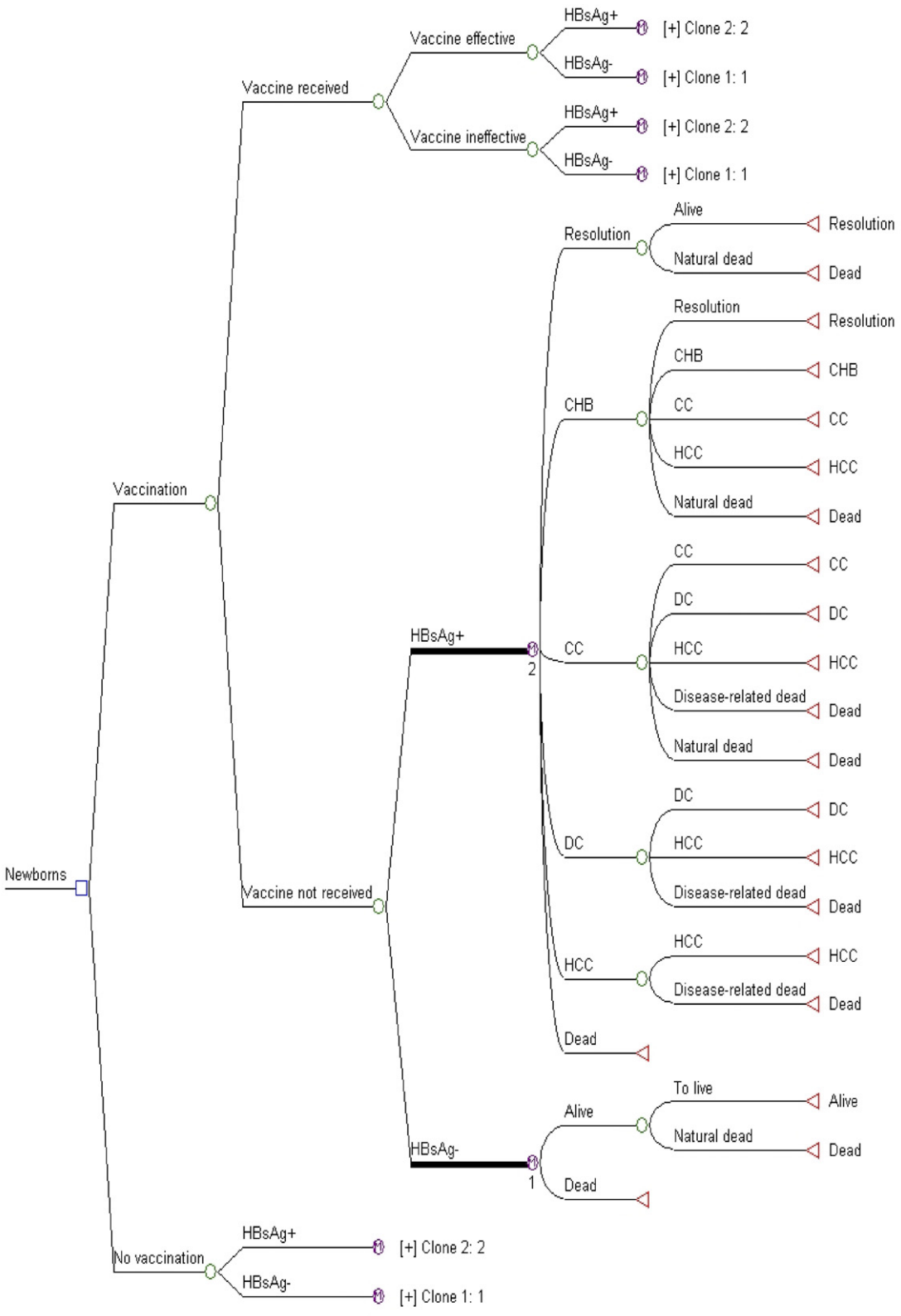

* CHB = Chronic hepatitis B; CC = Compensated cirrhosis; DC = Decompensated cirrhosis; HCC = Hepatocellular carcinoma; HBsAg = Hepatitis B surface antigen

Fig. 1 – Decision analytic model for estimating the cost-effectiveness of universal hepatitis B vaccination in Vietnam. CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HbsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

Table 1 – Base-case estimates and corresponding distributions for deterministic and probabilistic analyses.

Parameter	Base-case estimates	Range	Distribution	
Newborn immunization against HBV				
HBV prevalence (%)	14.70	8.80–20.50	Triangular	[6,7]
Vaccine coverage (%)	70.00	45.00–94.00	Triangular	[11]
Vaccine efficacy (%)	84.00	65.00–95.00	Triangular	[12–14]
Vaccine wastage (%)	12.50	5.00–25.00	Triangular	[11,15]
Immunization cost/child (US $)*	4.50	1.50–10.50	Triangular	[16,17]
Disease progression				
Outcome from chronic hepatitis B				
Resolution	0.006183		Gamma (26.56, 4295.75)	[18–20]
Chronic hepatitis B	#†			
Compensated cirrhosis	0.022989		Gamma (32.98, 11,434.66)	[21–25]
Hepatocellular carcinoma	0.009100		Gamma (10.27, 1128.91)	[18,20–22,24,26–29]
Disease nonrelated deaths	Life table		Beta	[30]
Outcome from compensated cirrhosis				
Compensated cirrhosis	#			
Decompensated cirrhosis	0.069139		Gamma (58.66, 848.48)	[31,32]
Hepatocellular carcinoma	0.016121		Gamma (5.72, 354.72)	[32]
Disease-related death	0.033146		Gamma (11.04, 333.05)	[3,23,33]
Disease nonrelated deaths	Life table		Beta	[30]
Outcome from decompensated cirrhosis				
Decompensated cirrhosis	#			
Hepatocellular carcinoma	0.05		None	[34]
Disease-related deaths	0.245262		Gamma (39.29, 160.21)	[35]
Outcome from hepatocellular carcinoma				
Survival	0.088710		Gamma (232.75, 2623.75)	[36,37]
Disease-related death	#			
Cost estimates (US $)				
Treatment cost (health care perspective)				
Chronic hepatitis B	270		Gamma (535.2326; 1.98155)	Data available upon request
Compensated cirrhosis	564		Gamma (348.5901; 0.61709)	
Decompensated cirrhosis	1559		Gamma (10,515.865; 6.74428)	
Hepatocellular carcinoma	1901		Gamma (13,148.086; 6.91638)	
Treatment cost (societal perspective)				
Chronic hepatitis B	347		Gamma (885.83; 2.55)	
Compensated cirrhosis	746		Gamma (607.98; 0.81)	
Decompensated cirrhosis	1774		Gamma (13,615.48; 7.67)	
Hepatocellular carcinoma	2111		Gamma (16,222.215; 7.68)	
Discount rate (%)	0 or 3			
Quality of life				
Chronic hepatitis B	0.92	0.90–0.98	Triangular	[38–40]
Compensated cirrhosis	0.82	0.75–0.95	Triangular	
Decompensated cirrhosis	0.55	0.25–0.75	Triangular	
Hepatocellular carcinoma	0.55	0.25–0.75	Triangular	

HBV, hepatitis B virus.

* The hepatitis B vaccine used for newborns in Vietnam was purchased through Global Alliance for Vaccines and Immunizations's financial support from 2002 to 2008. The cost of the vaccine alone was ~US $1 [16,17]. Including the administration costs, the full cost per dose was ~US $ 1.50 (range of US $0.5–3.5) [16,17].

† The hash mark (#) is used in place of the probability expression for one branch to have TreeAge Pro automatically calculate the complement during calculations.

ticle, we estimated the cost-effectiveness of the current HBV vaccination program in Vietnam. In addition, cost-effectiveness affordability curves were constructed to estimate the budget impact on the vaccination program.

Methods

Modeling approach

We designed a decision analytic model to estimate the cost-effectiveness of universal vaccination against HBV compared with no vaccination. A Markov model simulating disease progression was linked to a decision tree (Fig. 1). The analyses were performed by using the simulation software TreeAge Pro, version 2009.

In the model we focused only on CHB infections because chronic infections comprise the largest burden of the disease and published clinical data on acute and fulminant stages are currently lacking for Vietnam. The Vietnamese birth cohort of 2002 was selected because universal vaccination against HBV was completed in mid-2003; thus, we can compare the impact before and after universal HBV vaccination. Type 1 mortality was assumed (i.e., everyone lives to the life expectancy, which is 75 years in Vietnam). Each Markov cycle was defined as 1 year. The Markov

Table 2 – Base-case results for vaccination versus no vaccination strategies against HBV for newborns where the HBV carrier rate is 14.7%, vaccine coverage is 70%, vaccine efficacy is 84%, vaccine wastage is 12.5%, and discount rate is 3%.

Parameter	Unvaccinated cohort	Vaccinated cohort	Change with vaccination
HBV carrier rate (%)	14.70%	6.04%	−8.66%
Discounted expected life-years per person	27.21	28.01	0.80
Discounted QALY gained per person	26.94	27.90	0.95
No. of new infections for the cohort	240,114	98,927	−141,187
No. of primary liver cancer cases	2,185	900	−1,285
No. of premature deaths	2,366	975	−1,391
Lifetime cost incurred from societal perspective (US $) per person	1,151.52	478.03	−673.49
Lifetime cost incurred from health care perspective (US $) per person	910.00	378.00	−532.00
Cost incurred from payer's perspective (US $) per person		3.60	
ICER per LYG (US $) from payer's perspective		4.52	
ICER per QALY gained (US $) from payer's perspective		3.77	
Cost of preventing a HBV carrier		41.79	
Total vaccination cost of birth cohort (US $)		5,900,400	

HBV, hepatitis B virus; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

health states used in the model were alive, immunity, CHB, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and death.

Parameters

Probabilities

The transition probabilities used in the model represent the natural course of CHB infections and were obtained from international literature (through PubMed), particularly from studies in high-endemic Asian countries where the epidemiology of hepatitis B infections is more similar to that of the Vietnamese situation (Table 1). When there were two or more studies reporting estimates for a particular transition probability, we combined the outcomes of the studies by using a random effect model to account for possible heterogeneity [41].

Other parameters (hepatitis B surface antigen carrier prevalence, vaccine coverage, vaccine efficacy, and vaccine wastage) are also presented in Table 1.

Cost estimates

The cost-effectiveness analysis was performed from societal, health care, and payer's perspectives. For the societal perspective, we included direct medical costs (vaccination cost and the averted costs of treatment for CHB infections), direct nonmedical costs (travel, meals, and lodging), and indirect costs (productivity loss). For the health care perspective, only direct medical costs were included. For the payer's perspective, where the Vietnamese government or international organizations are the main payers for vaccination programs, we included only the vaccination cost (Table 1).

Treatment cost of CHB and its related progressions was taken from a previous cost-of-illness study we conducted for Vietnam (data are available upon request). All costs were reported in US $ (US $1 =17,803 VND [42]) and adjusted for inflation by using the country's gross domestic product deflators (Table 1).

Quality of life

Because of a lack of data on specific quality-of-life estimates for Vietnam, quality-of-life estimates were based on various international sources (Table 1).

Other assumptions

In the model we made several assumptions: 1) all CHB infections occurred in the first year of life, 2) the mortality and losses of quality-adjusted life-year (QALY) and life-years gained that were due to acute hepatitis B infections were ignored, 3) the simulation continued until 99.9% of the cohort had deceased, and (iv) the hepatitis B unrelated death rate was based on the age-specific mortality of the Vietnamese population [30]. In the absence of 2002 age-specific mortality rates, we used the rates from 2006 assuming that mortality rates remained constant between 2002 and 2006.

Sensitivity analysis

To evaluate parameter uncertainties, we conducted univariate sensitivity analyses (results from only the payer's perspective are shown) and probabilistic sensitivity analyses for all the three perspectives. For the latter, we conducted 5000 Monte Carlo simulations. Distributions associated with input parameters are shown in Table 1 [43]. The results were subsequently presented in a cost-effectiveness acceptability curve (CEAC) from the payer's perspective only. We then evaluated affordability on the basis of joint distribution of simulated incremental costs and health gains of HBV vaccination. Affordability analysis was done with

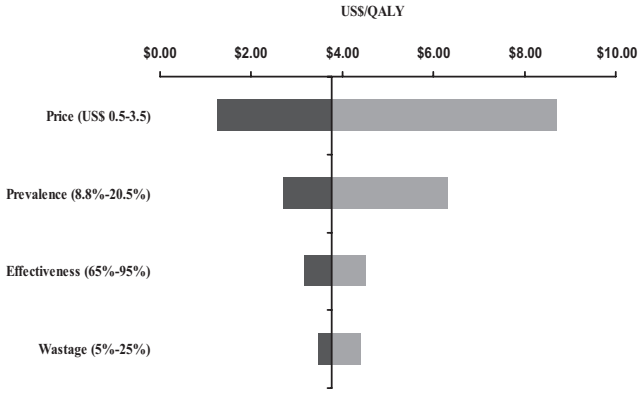

Fig. 2 – Results of univariate sensitivity analyses showing the ranges of ICERs for universal newborn HBV vaccination compared with no vaccination in Vietnam (payer's perspective). HBV, hepatitis B virus; ICERs, incremental cost-effectiveness ratios; QALY, quality-adjusted life-year.

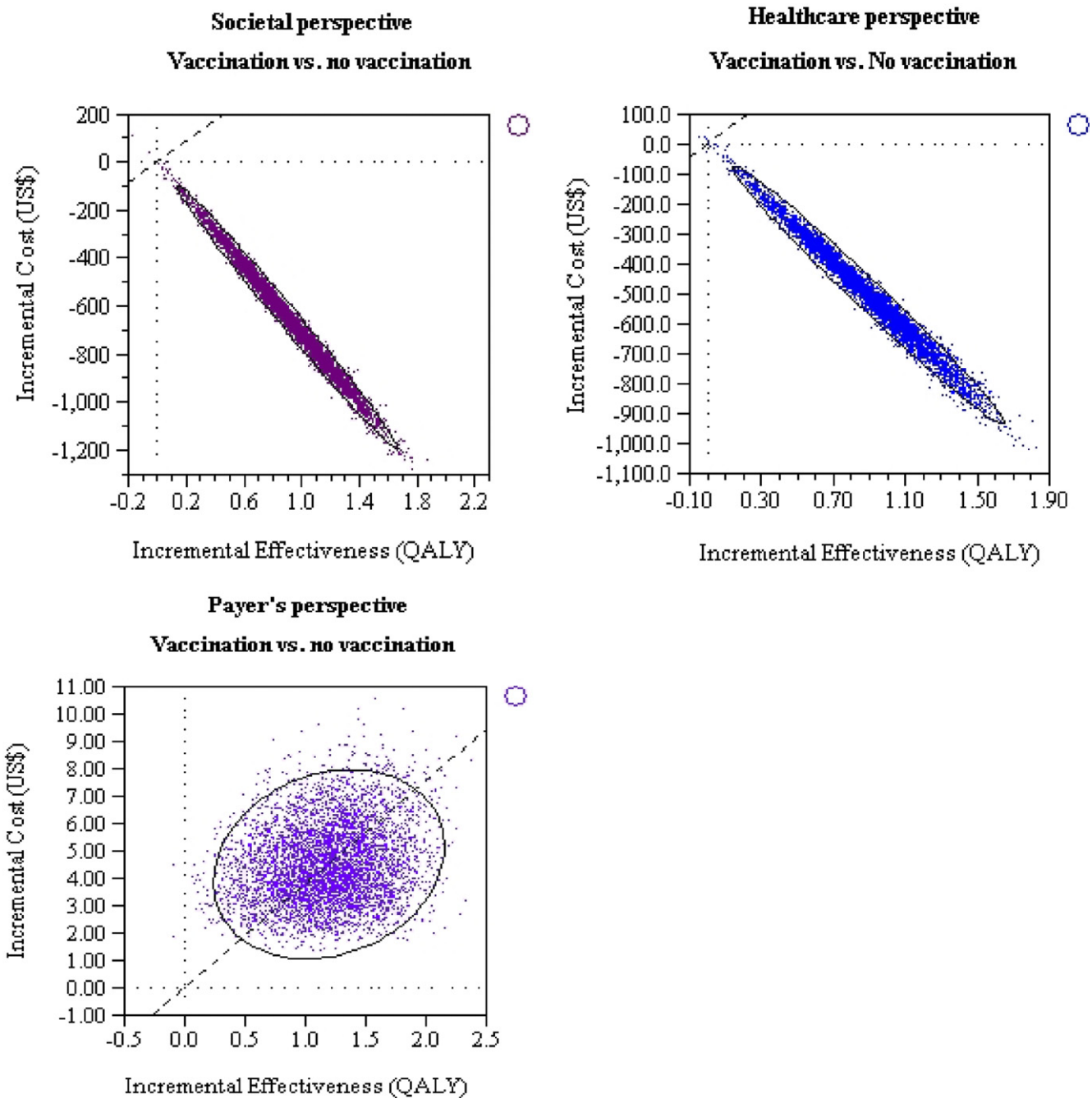

Fig. 3 – A total of 5000 Monte Carlo simulations of incremental cost-effectiveness ratios plotted on a cost-effectiveness plane comparing vaccination versus no vaccination. QALY, quality-adjusted life-year.

the assumption that vaccination programs for infants were indivisible, which means it cannot be done for only a fraction of infants because in Vietnam universal hepatitis B vaccination is for every child. By using the theory and methodology described by Sendi and Briggs [44], we generated a CEAC by capturing the points in the cost-effectiveness plane under the horizontal lines representing different budget levels.

Outcome measurement

Life-years gained, QALY, and incremental cost-effectiveness ratios per life-year gained and per QALY for different scenarios (vaccination vs. no vaccination) were calculated.

Results

Results of the base-case analyses comparing universal HBV vaccination with no vaccination are presented in Table 2. Vaccination is highly cost-effective from the payer's perspective and cost-saving from societal and health care perspectives.

Univariate sensitivity analyses (shown only for the payer's perspective) showed that incremental cost-effectiveness ratios were most sensitive to vaccine price and HBV prevalence (Fig. 2). Probabilistic sensitivity analyses results are demonstrated on cost-effective planes, confirming that universal vaccination dominates no vaccination from societal and health care perspectives (Fig. 3).

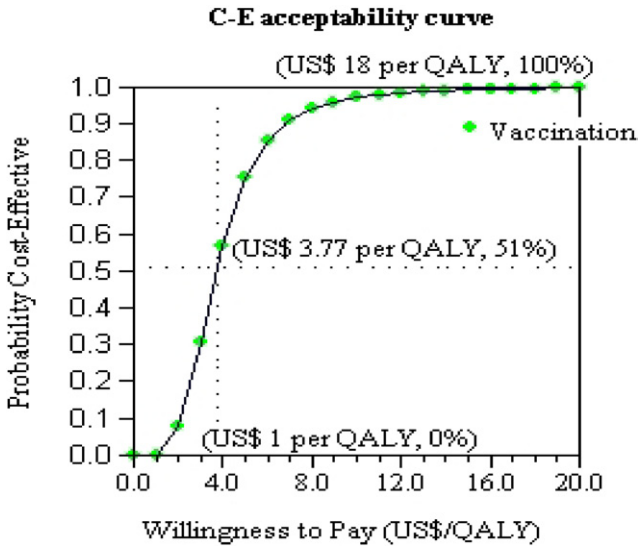

Fig. 4 – Cost-effectiveness (C–E) acceptability curve showing that the probability of universal newborn vaccination against HBV in Vietnam is cost-effective at different cost-effective threshold values (payer's perspective). HBV, hepatitis B virus; QALY, quality-adjusted life-year.

Subsequently, a CEAC (only for the payer's perspective) was derived, reporting that at the base-case threshold (US $3.77 per QALY), the cost-effectiveness probability for the vaccination program was 51%. At the willingness-to-pay (WTP) threshold of US $18 per QALY, the cost-effectiveness probability reached 100%, but it decreased to 0% when the WTP threshold was less than US $1 per QALY (Fig. 4).

Furthermore, affordability curves were generated to explain the impact of financial resources on the vaccination program. We explicitly assessed the impact of the budget on vaccination alone; thus, all affordability and cost-effectiveness affordability analyses were evaluated from the payer's perspective. The results indicated

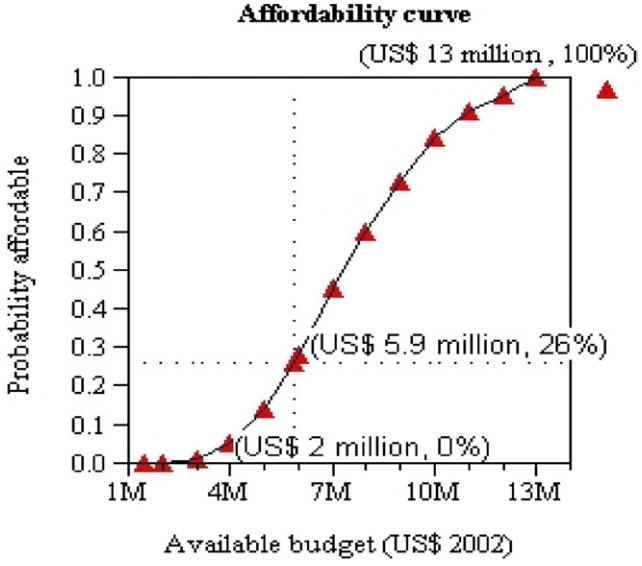

Fig. 5 – Affordability curve showing the impact of financial resources on the universal newborn HBV vaccination program in Vietnam (payer's perspective). HBV, hepatitis B virus.

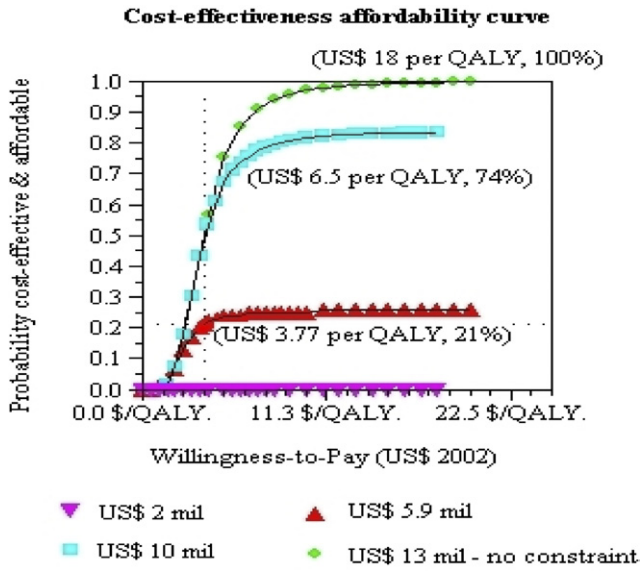

Fig. 6 – Cost-effectiveness (C–E) and affordability curve presenting various scenarios for universal newborn HBV vaccination in Vietnam being both cost-effective and affordable at different cost-effective threshold values and budgets (payer's perspective). HBV, hepatitis B virus; QALY, quality-adjusted life-year.

that vaccination would not be affordable when the budget is less than US $2 million but always implementable when the budget exceeds US $13 million (Fig. 5). For the base-case at the US $5.9 million budget per year (Table 2), the probability for the program being affordable was only 26% because of the uncertainties surrounding the program cost.

Combining the CEAC and the affordability curve, the cost-effectiveness affordability curve presented various scenarios for a vaccination program being both cost-effective and affordable at different cost-effective threshold values and budgets (Fig. 6). If the budget is less than US $2 million, the probability for the vaccination program to be cost-effective and affordable is 0%, regardless of the WTP threshold. In the base-case scenario with a cost-effective threshold of US $3.77 per QALY and the US $5.9 million budget, the probability was 21%. The vaccination program would be 100% cost-effective and affordable when the budget reaches US $13 million and the WTP threshold reaches US $18 per QALY.

Discussion

The results from the base-case analyses showed that universal newborn HBV vaccination could reduce the HBV carrier rate by ~60%. Using the World Health Organization's criteria for cost-effectiveness [45], our analyses suggest that HBV vaccination in Vietnam is highly cost-effective from the payer's perspective and a cost-saving intervention from both societal and health care perspectives. The incremental cost-effectiveness ratio was only US $3.77 per QALY, which is much lower than 3× Vietnamese per-capita gross domestic product in 2002 [46]. The cost-effectiveness of the program was most sensitive to vaccine price and HBV prevalence.

At the country's per-capita GDP of ~US $440 in 2002 [46] and the assumed cost of US $4.5 per fully immunized child, vaccination remained an acceptable and affordable option even for a Vietnamese household to pay out of pocket. However, with an annual birth cohort of 1,639,000, HBV vaccination could become a large invest-

ment for the Vietnamese government. Thus, the cost of universal vaccination poses a heavy financial burden when the Global Alliance for Vaccines and Immunizations's support for Vietnam in the Expanded Program of Immunization is terminated. This financial implication should prompt the Vietnamese health decision makers to access the processes involved in setting priorities and allocating limited resources among different childhood vaccination programs. In this context, the importance of examining affordability and cost-effectiveness of large-scale health programs should be taken in consideration. The strength of affordability analysis is its accountability of uncertainties of health and effects by running probabilistic sensitivity analyses. It assists policymakers to estimate the affordable probability of a vaccination program under a specific budget and to look for external resources if the government cannot finance the program itself. In details, the affordability curve estimated that the newborn HBV vaccination in Vietnam could start as low as US $2,100,000 but becomes 100% cost-effective and affordable with an annual budget of at least US $13 million. Even at this maximum level of investment, the program cost is extremely modest in comparison to the treatment costs of CHB infections in Vietnam. In addition, vaccination will gradually reduce HBV prevalence in Vietnam. Therefore, continuing the vaccination program appears to be a wise health investment. Using affordability as a tool to forecast the needed budget also aids the Vietnamese government in the application for further financial support from the Global Alliance for Vaccines and Immunizations.

Naturally, our study has a few limitations. First, we applied a simple static Markov model of the disease instead of a dynamic model. Because of the lack of data and information, we opted to focus only on the chronic part of the hepatitis B infection and ignored the acute and fulminant stages. However, morbidity from these clinical presentations was short-lasting and mortality constituted only a small proportion of hepatitis B–related deaths, but their inclusion in our model would likely make HBV vaccination even more cost-effective. Second, because of an absence of published epidemiological data on hepatitis B in Vietnam, we used published data from other countries in the region where extensive research on the disease had been conducted [19,25,28,29,35], or data from the Western world (in the cases where no data were available at all). This is justified because disease progression rates appear to be stable across populations. Third, we did not have the age-specific disease progression rate and we assumed the same prevalence rate for all age groups. This might underestimate the number of infections that would occur in this birth cohort and that current prevalence is a rough estimate for infections that might occur to the population. Fourth, the study did not take into account the indirect herd-immunity effects; doing so again would likely make HBV vaccination more cost-effective.

As the first cost-effectiveness study on universal newborn vaccination in Vietnam, the outcomes are very encouraging and informative. The results might assist policymakers in motivating the continued support for universal HBV vaccination. Our findings will also be informative for health-policy decisions in other high-endemic countries of HBV prevalence. In addition, our study demonstrated that next to conducting cost-effectiveness analysis of large-scale intervention programs, cost-effectiveness affordability curves can be used for resource planning of health interventions, especially for new and underused vaccines. To fully evaluate the impact of HBV vaccination in Vietnam, future studies applying dynamic models of HBV infection to account for herd immunity and acute and fulminant stages of the disease are recommended.

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